Docket No.
484-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thomas Cremers, et al. Confirmation No. 5528

Application No.: 10/596,348 Group Art Unit: 1614

Filed: July 14, 2006 Examiner: Rao, Savitha

For: THE COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND A HISTAMINE H3 RECEPTOR ANTAGONIST, INVERSE AGONIST OR PARTIAL AGONIST

Date: August 10, 2009

DECLARATION OF CONNIE SÁNCHEZ MORILLO, D. SC., PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Connie Sánchez Morillo, D. Sc., hereby declare as follows:

1. I am an expert in the field of the present invention as evidenced by my Curriculum Vitae, attached as Exhibit A.

2. I have reviewed the subject patent application which discloses the combination administration of a serotonin reuptake inhibitor and a histamine H3 receptor antagonist, inverse agonist or partial agonist. I have also reviewed the Office Action issued February 20, 2009, and present claims 1, 5-21, and 35-36, in connection with the subject patent application.

3. The subject application discloses that co-administration of a high-affinity H3 receptor antagonist and a serotonin reuptake inhibitor produces a significant increase in the level of serotonin in terminal areas (of the brain), as compared to the administration of the serotonin reuptake inhibitor alone. See page 19, lines 1-4 of the subject application as filed. The subject application discloses that the administration of H3 antagonist alone causes no increase in serotonin levels. The subject application further discloses that serotonin (5-HT) levels were measured in microdialysis experiments. See page 28, line 5 through page 30, line 15 of the subject application as filed.

4. As disclosed in the subject application, the combination of a H3 receptor antagonist and a serotonin reuptake inhibitor elicits an unexpected synergistic effect on the central nervous

system (CNS). It was not obvious at the time of filing the subject application that the combination of a H3 receptor antagonist and a serotonin reuptake inhibitor would be synergistic.

5. In support of my statement made in the preceding paragraphs three and four, I submit the following:

(a) Experiments were conducted in the laboratories of University of Groningen to assess the effects of co-administration of thioperamide or ciproxifan, both high-affinity H3 receptor antagonists, and citalopram, a serotonin reuptake inhibitor. Extracellular levels of 5-HT were measured in the ventral hippocampus of rats following:

(i) subcutaneous (s.c.) administration of citalopram (10 µmol/kg),

(ii) subcutaneous (s.c.) administration of thioperamide (12.25 µmol/kg[1]),

(iii) co-administration of citalopram (10 µmol/kg s.c.) plus thioperamide (12.25 µmol/kg s.c.),

(iv.) subcutaneous (s.c.) administration of ciproxifan (15 mg/kg),

(v.) co-administration of citalopram (10 µmol /kg s.c.) plus ciproxifan (15 mg/kg s.c.), and

(vi.) co-administration of citalopram (10 µmol /kg s.c.) plus ciproxifan (1 mg/kg s.c.).

(b) Elevated 5-HT levels were measured in dialysates by microdialysis at each 15-minute interval following administration (injection = time zero). Microdialysis techiniques are well-known in the art.

(c) The level of 5-HT in each dialysate was compared and plotted over a period of 150 minutes. See the figures attached hereto as Exhibits B and C.

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[1] 12.25 µmol/kg = 5 mg/kg based on molecular weight (MW) of thioperamide (Sigma-Aldrich Catalog #T123, CAS # 148440-81-7, MW = 408).

6. In the experiments as represented in the attached figure (Exhibit B), administration of thioperamide alone (12.25 µmol/kg; -▲- Exhibit B) demonstrated baseline levels of 5-HT. 100% of baseline levels means that no increase or decrease was observed above the normal baseline levels of 5-HT in the hippocampus of the rat, such normal baseline levels being observed prior to administration of any drug (see -▲- Exhibit B). In these experiments, administration of citalopram alone (10 µmol/kg; -■-) demonstrated an increase over baseline to nearly 500% of baseline 5-HT levels within 45 minutes and steadying to these levels for 150 minutes. These experiments further demonstrated that co-administration of citalopram (10 µmol/kg s.c.) plus thioperamide (12.25 µmol/kg) elicited a significantly greater increase, e.g. approximately 900% of baseline 5-HT levels, at time intervals of 75, 90, 105, and 150 minutes following injection (see -●- Exhibit B, and page 30, lines 1-6 of the specification).

7. Since thioperamide alone fails to elicit 5-HT levels above baseline, then the additive effect of the co-administration of citalopram plus thioperamide on 5-HT levels is expected to be the same as citalopram alone, or 5-HT levels aproximately 500% of baseline. The co-administration of citalopram plus thioperamide, however, consistently elicited a much greater increase over baseline 5-HT levels, e.g. 900% of baseline, when compared to the effect of citalopram alone. This greater increase in 5-HT levels induced by co-administration citalopram and thioperamide is evidence of an unexpected synergistic effect.

8. Similarly, co-administration of citalopram (10 µmol/kg s.c.) plus ciproxifan (15 mg/kg) elicited a significantly greater increase, e.g. over 1000% of baseline 5-HT levels, at time intervals of 60, 75, 90, 105, 120 and 135 minutes following injection (see -▼- Exhibit C, and page 30, lines 10-15 of the specification).

9. Given the prior art teachings, one would not conclude that H3 antagonists, inverse agonists or partial agonists, and serotonin reuptake inhibitors produce a synergistic effect, let alone an additive effect, on serotonin levels in the brain. There is no prior art evidence of increased serotonin levels as induced by H3 receptor antagonism or inhibition.

10. It is generally known and accepted in the art that inducing an elevation of serotonin levels

in the brain leads to more efficacious antidepressants. By administering H3 receptor antagonists, inverse agonists or partial agonists in combination with a serotonin reuptake inhibitor, these H3 receptor inhibitors may be used to augment the effect of the serotonin reuptake inhibitor by causing such further increase of 5-HT levels. Through this synergistic effect, H3 antagonists, inverse agonists or partial agonists provide significant improvement to the therapeutic effect (efficacy) of a serotonin reuptake inhibitor like citalopram.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

08/10/09

Date

Connie Sánchez Morillo, D. Sc.

CURRICULUM VITAE

Connie Sánchez (Morillo)

Current responsibilities:

Vice President, Neuroscience, Lundbeck Research, USA, Inc.

Previous responsibilities (H.Lundbeck A/S):

2001-2004. Manager of the escitalopram (Cipralex®) pharmacology research team, team task to investigate in depth the mechanism of action of escitalopram.

1999-2001. Head of department of neuropharmacology, which is responsible for in vivo epilepsy research and sleep research.

1997-1999. Head of in vivo screening department, which was responsible for in vivo screening models of anxiety, depression and psychosis.

1995-1997. Research manager for drug discovery projects within depression and anxiety.

1986-1995. Scientist and senior scientist in Pharmacological Research Departments and responsible for establishment of animal models of anxiety and depression

1981-1986. Clinical Research Department as research fellow and project manager

Other employment:

1980-1981. Practising histology (methods, techniques and diagnostics) at Cátedra de Histología, Facultad de Medicina, University of Barcelona, Spain.

1978-1980. Flavour chemist analysing and composing food flavours at Grindsted Products A/S, Brabrand, Denmark.

University degrees:

M Sc & D Sc. Pharmacology

Scientific societies, working groups and other academic activities:

Member, previous board member and secretary of Danish Society of Pharmacology and Toxicology. Member of Danish Society of Neuroscience, European Behavioural Pharmacology Society, Scandinavian Society of Psychopharmacology, International Society of Psycho-Neuro-Endocrinology, and Society of Neuroscience.

Member of various working groups designing post graduated courses (statistics, pharmacology and physiology at basic and advanced levels) for laboratory personnel.

Ph D and M Sc students. Approved as external examiner at the University of Copenhagen. Lecturing at postgraduate courses at the Pharmaceutical and Veterinarian and Agricultural Universities.

Referee for European Journal of Pharmacology, Neuropsychopharmacology, Neuropharmacology, Pharmacology Biochemistry and Behaviour, Pharmacology and Toxicology, Psychopharmacology, Behavioural Brain Research, Brain Research, Physiology and Behaviour, European Journal of Neuroscience, Journal of Neural Transmission, Journal of European Neuropsychopharmacology.

Publications:

More than 80 publications in peer reviewed journal, more than 200 abstracts and poster presentations, more than 100 oral presentations at symposia and several use patents.

Patent Publications:

1. US Patent No. 6,262,061, issued July 17, 2001, entitled "Treatment of panic attacks"
2. US Patent No. 6,358,966, issued March 19, 2002, entitled "Treatment of depression"
3. PCT International Application Publication No. WO2002/102387, published on December 27, 2002, entitled "Treatment of neuropathic pain"
4. US Patent Application Publication No. US20040029957 A1, published February 12, 2004 entitled "Treatment of Neurotic Disorders"
5. US Patent Application Publication No. US20040029958 A1, published February 12, 2004 entitled "Treatment of Neurotic Disorders"
6. US Patent Application Publication No. US20040192764A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
7. US Patent Application Publication No. US20040192765A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
8. US Patent Application Publication No. US20040192766A1, published September 30, 2004 entitled "Use of enantiomeric pure escitalopram"
9. US Patent Application Publication No. US20040198809A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
10. US Patent Application Publication No. US20040198810A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
11. US Patent Application Publication No. US20040198811A1, published October 7, 2004 entitled "Use of enantiomeric pure escitalopram"
12. US Patent Application Publication No. US20050234093A1, published October 20, 2005 entitled "Gaboxadol for treating depression and other affective disorders"
13. US Patent No. 6,960,613, issued November 1, 2005, entitled "Treatment of neurotic disorders"
14. US Patent Application Publication No. US20050288371A1, published December 29, 2005 entitled "Treatment of neuropathic pain, fibromyalgia or rheumatoid arthritis"
15. US Patent Application Publication No. US20070117844A1, published May 24, 2007 entitled "5-HTP Combination Therapy"
16. US Patent Application Publication No. US20070123584A1, published May 31, 2007 entitled "A method of treating premenstrual dysphoric disorder with escitalopram"
17. US Patent No. 7,265,151, issued September 4, 2007, entitled "Treatment of neurotic disorders"

18. US Patent No. 7,271,194, issued September 18, 2007, entitled "Treatment of neurotic disorders"
19. US Patent Application Publication No. US20070213370A1, published September 13, 2007 entitled "5-HTP Combination Therapy"
20. US Patent Application Publication No. US20070276035A1, published November 29, 2007 entitled "Treatment of neurotic disorders"
21. US Patent Application Publication No. US20080004338A1, published January 3, 2008

Publications:

1. Gram LF et al. (1986). Clinical effect profile in comparison with clomipramine. A controlled multicenter study. Psychopharmacol. 90, 131-138.
2. Timmerman L, De Beurs P, Tan BK, Leijnse-Ybema H, Sánchez C, Høpfner Petersen HE and Cohen-Stuart MH (1987). A double-blind comparative clinical trial of citalopram vs maprotiline in hospitalized depressed patients. Int. Clin. Psychopharmacol. 2, 239-253.
3. Hyttel J, Arnt J, Bøgesø KP, Christensen AV, Larsen J-J, Lembøl HL, Meier E and Sánchez C (1988). Neurochemical and behavioural profile of Lu 17-133, (+)-trans-4-[3-(3,4-dichlorophenyl)-indan-1-yl]-1-piperazine ethanol, an inhibitor of the uptake of dopamine and noradrenaline. Drug Dev. Res. 13, 213-230.
4. Sánchez C (1989). The effects of dopamine D_1 and D_2 receptor agonists on body temperature in male mice. Eur. J. Pharmacol. 171, 201-206.
5. Sánchez C, Arnt J, Dragsted N, Hyttel J, Lembøl HL, Meier E, Perregaard J, and Skarsfeldt T (1991). Neurochemical and in vivo pharmacological profile of sertindole, a limbic-selective neuroleptic compound. Drug Devel. Res. 22, 239-250.
6. Arnt J, Hyttel J and Sánchez C (1992). Partial and full dopamine D_1 receptor agonists in mice and rats: relation between behavioural effects and stimulation of adenylate cyclase activity in vitro. Eur. J. Pharmacol. 213, 259 - .
7. Arnt J, Sánchez C and Skarsfeldt T (1992). Relevance of drug discrimination methods for the evaluation of antipsychotic drugs. Eur. Neuropsychopharmacol. 2, 223-224.
8. Hyttel J, Arnt J, Costall B, Dragsted N, Lembøl HL, Meier E, Naylor RJ, Nowak G, Sánchez C and Skarsfeldt T (1992). Clin. Neuropharmacol. 15, suppl. I, 267-268.
9. Hyttel J, Bøgesø KP, Perregaard J and Sánchez C (1992). The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J. Neural. Transm. 88, 157-60.
10. Perregaard J Arnt J, Bøgesø K and Sánchez C (1992). Non-cataleptogenic centrally acting dopamine D_2 and serotonin 5-HT_2 antagonists within a series of 3-substituted 1-(4-fluorphenyl)-1H-indoles. J. Med. Chem. 35, 1092-1101.
11. Perregaard J, Andersen K, Hyttel J and Sánchez C (1992). Selective centraly acting serotonin 5-HT_2 antagonists. Part I: 2- and 6- substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles. 35, 4813-4822.
12. Sánchez C and Arnt J (1992). Effects on body temperature in mice differentiates between dopamine D_2 receptor agonists with high and low efficacies. Eut. J. Pharmacol. 211, 9-14.
13. Perregaard J Sánchez C and Arnt J (1993). Recent development in anxiolytics. Cur. Opin. Ther. Pat. 1, 101-128.
14. Sánchez C (1993). Effect of serotonergic drugs on footshock-induced ultrasonic vocalization. Behav. Pharmacol. 4, 269-277.

15. Sánchez C and Meier E (1993). Central and peripheral mediation of hypothermia, tremor and salivation induced by muscarinic agonists in mice. Pharmacol. Toxicol. 72, 262-267.

16. Sánchez C, Arnt J, Hyttel J and Moltzen E (1993). The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. Psychopharmacol. 110,53 -59.

17. Arnt J, Sánchez C and Skarsfeldt T (1994). The so-called atypical antipsychotics-How similar are they? Neuropsychopharmacology, 10, 469S.

18. Domeney AM, Arnt J, Costall B, Naylor RJ, Sánchez C and Smith AG (1994). Effect of sertindole on raised mesolimbic dopaminergic activity in the rat. Drug Devel. Res. 31, 175-185.

19. Moltzen EK, Pedersen H, Bøgesø KP, Meier E, Frederiksen K, Sánchez C, and Lembøl HL (1994). Bioisosteres of arecoline: 1,2,3,6-tetrahydro-5-pyridyl-substituted and 3-piperidyl-substituted derivatives of tetrazoles and 1,2,3-triazoles. Synthesis and muscarinic activity. J. Med. Chem. 37, 4085-4099.

20. Sánchez C (1994). Sertindole- an atypical neuroleptic. *In* Strategies for studying brain disorders (eds Palomo, T., Archer, T. And Beninger, R.) , 2, 157-163.

21. Sánchez C and Hyttel J (1994). Isolation-induced aggression in mice: Effects of 5-hydroxytryptamine uptake inhibitors and involvement of postsynaptic 5-HT_{1A} receptors. Eur. J. Pharmacol. 264, 241-247.

22. Sánchez C and Lembøl HL (1994). The involvement of muscarinic receptor subtypes in the mediation of hypothermia, tremor and salivation in male mice. Pharmacol. Toxicol. 74, 35-39.

23. Arnt J, Sánchez C, Lenz SM, Madsen U and Larsen PK (1995). Differentiation of in vivo effects of AMPA and NMDA receptor ligands using drug discrimination methods and convulsants / anticonvulsant activity. Eur. J. Pharmacol. 285, 289-297.

24. Hyttel J, Arnt J and Sánchez C (1995). The pharmacology of citalopram. Rev. Contemp. Pharmacother. 6, 271-285.

25. Nielsen CK and Sánchez C (1995). Effect of chronic diazepam treatment on footshock-induced ultrasonic vocalization in adult male rats. Pharmacol. Toxicol. 77, 177-181.

26. Perregaard J, Moltzen EK, Meier E and Sánchez C (1995). ligands with subnanomolar affinity and preference for the σ_2 binding site. 1. 3-(ω-aminoalkyl)-1H-indoles. J. Med. Chem. 38, 1998-2008.

27. Sánchez C (1995). Serotonergic mechanisms involved in facilitation of exploratory behaviour of mice in a fully automated two compartment black and white test box. Pharmacol. Toxicol. 77, 71-78.

28. Sánchez C, Arnt J, Costall B, Domeney AM, Kelly E and Naylor RJ (1995). Sertindole: A limbic selective neuroleptic with potent anxiolytic effects. Drug Devel. Res. 34, 19-29.

29. Sánchez C (1996). 5-HT_{1A} receptors play an important role in modulation of behavior of rats in a two-compartment black and white box. Behav. Pharmacol. 7, 1-10.

30. Sánchez C, Arnt J and Moltzen E (1996). Assessment of relative efficacies of 5-HT_{1A} receptor ligands by means of in vivo animal models. Eur. J. Pharmacol. 315, 245-254.

31. Sánchez C, Arnt J and Moltzen EK (1996). The antiaggressive potency of (-)-penbutolol involves both 5-HT_{1A} and 5-HT_{1B} receptors and □-adrenoceptors. Eur. J. Pharmacol. 297, 1-8.

32. Hansen HH, Sánchez C and Meier E (1997). Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced

immobility in adult rats: A putative animal model of depression. J. Pharm. Exp. Ther. 283(3), 1333-1341.

33. Sánchez C (1997). Acute stress enhances anxiolytic-like drug responses of mice tested in a black and white test box. Eur. Neuropsychopharm. 7, 283-288.

34. Sánchez C (1997). Interaction studies of 5-HT_{1A} receptor antagonists and selective 5-HT reuptake inhibitors in isolated aggressive mice. Eur. J. Pharmacol. 334, 127-132.

35. Sánchez C and Meier E (1997). Behavioral profiles of SSRIs in animal models of depression, anxiety and aggression. Are they all alike? Psychopharmacol. 129, 197-205.

36. Sánchez C, Arnt J, Costall B, Kelly ME, Meier E, Naylor RJ and Perregaard J (1997). The selective □$_2$-ligand Lu 28-179 has potent anxiolytic-like effects in rodents. J. Pharm. Exp. Ther. 283 (3), 1343-.

37. Sánchez C (1998). 5-HT_{1A} receptors in the treatment of aggression and impulse control disorders (ICDs), *in* Maes,M. And Coccaro, E.F. (Eds) Neurobiology and clinical views on aggression and impulsivity. John Wiley & Sons Ltd, UK.

38. Sánchez C, Arnt J, Didriksen M Dragsted N, Lenz SM and Marz J (1998). In vivo muscarinic cholinergic mediated effects of Lu 25-109, a M_1 agonist and M_2/M_3 antagonist. Psychopharmacol. 137, 233-240.

39. Jensen JB, Jessop DS, Harbuz MS, Mørk A and Sánchez C and Mikkelsen JD (1999). Acute and long-term treatments with the selective serotonin reuptake inhibitor, citalopram, modulate the HPA axis activity at different levels in male rats. J. Neuroendocrin. 11, 465-471.

40. Sánchez C and Hyttel J (1999). Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell. Mol. Neurobiol. 19, 467-489.

41. Sánchez C and Mørk A (1999). EEDQ studies of the role of 5-HT_{1A} and 5-HT_2 receptors in mediation of foot-shock-induced ultrasonic vocalisation in adult rat. Eur. Neuropsychopharmacol. 9, 287-294.

42. Falch E, Perregard J, Frølund B, Søkilde B, Buur A, Hansen LM, Frydenvang K, Brehm L, Bolvig T, Larsson OM, Sanchez C, Schousboe A, Krogsgaard-Larsen P (2000). Selective inhibitors of glial GABA uptake: synthesis, absolute stereochemistry and pharmacology of the enantiomers of 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-bezisoxazole (exo-THPO) and analogues (1999). J. Med. Chem. 42, 5402-5414.

43. Joubert A, Sánchez C and Larsen F (2000). Citalopram. Human Psychopharmacology, 15, 439-451.

44. Kehler J, Hansen HI and Sánchez C 2000). Novel phosphinic and phosphonic acid analogues of the anticonvulsant valproic acid. Biorg. Med. Chem. Lett. 10(22), 2547-2548.

45. Kelliher P, Connor TJ, Harkin-A, Sánchez C, Kelly JP and Leonard BE (2000). Varying response to the rat forced swim test under diurnal and nocturnal conditions. Physiol. Behav. 69 (4-5), 531-539.

46. Nielsen CK, Arnt A and Sánchez C (2000). Intracranial self-stimulation and sucrose intake differ as hedonic measures following chronic mild stress: interstrain and interindividual differences. Behavioural Brain Research. 107, 21-33.

47. Sánchez C and Arnt J (2000). *In vivo* assessment of 5-HT_{2A} and 5-HT_{2C} antagonistic properties of newer antipsychotics. Behavioural Pharmacology 11, 291-298.

48. Sánchez C and Papp M (2000). The selective □$_2$ ligand Lu 28-179 has an antidepressant-like profile in the rat chronic mild stress model. Behavioural Pharmacology. 11, 117-124.

49. Madsen U, Bräuner-Osborne H, Frydenvang K, Hvene L, Johansen TN, Nielsen B, Sánchez C, Stensbøl TB, Bischoff F and Krogsgaard-Larsen P (2001). New class of selective antagonists of group I metabotropic glutamic acid receptors. J. Med. Chem. 44, 1051-1059.

50. Madsen U, Stensbøl TB, Bräuner-Osborne H and Sánchez C (2001). Fra krampefremkaldende til krampestillende effekt. Lægemiddelforskning. Danmarks farmaceutiske Højskole.

51. Montgomery SA, Loft H, Sánchez C, Reines EH and Papp M (2001). Escitalopram (S-enantiomer of citalopram) – clinical efficacy and onset of action predicted from a rat model. Pharmacol & Toxicol, 88(5), 282-286.

52. Montgomery SA, Loft H, Sánchez C, Reines EH, Papp M (2001). Letter to the editor. Pharmacol. Toxicol. 89, 154-155.

53. Frølund B, Jørgensen AT, Tagmose L, Stensbøl TB, Vestergaard HT, Engblom C, Kristiansen U, Sanchez C, Krogsgaard-Larsen P (2002). Novel class of potent 4-arylalkyl substituted 3-isoxazolol GABA(A) antagonists: synthesis, pharmacology, and molecular modeling. J. Med. Chem. 45, 2454-2468.

54. Papp M, Nalepa I, Antkiewicz-Michaluk L and Sánchez C (2002). Behavioural and biochemical studies of citalopram and WAY 100.635 in rat chronic mild stress model. Pharm, Biochem and Behav. 72, 465-474.

55. Vogel V, Sanchez C and Jennum P (2002). EEG measurements by means of radiotelemetry after intracerebroventricular (ICV) cannulation in rodents. J Neurosci Methods. J. Neurosci. Meth. 118, 89-96.

56. Kelliher P, Kelly JP, Leonard BE and Sánchez C (2003). Effects of acute and chronic administration of selective monoamine re-uptake inhibitors in the rat forced swim test. J Psychoneuroendocrinology. 28, 332-347.

57. Mørk A, Kreilgaard M, Sánchez C (2003). The R-enantiomer of citalopram counteracts escitalopram-induced increase in extracellular 5-HT in the frontal cortex of freely moving rats. Neuropharmacology, 45, 167-173.

58. Sánchez C (2003). R-citalopram attenuates anxiolytic effects of escitalopram in a rat ultrasonic vocalisation model. Eur J pharmacol. 464 (2-3), 155-158.

59. Sánchez C (2003). Stress-induced vocalisation in adult animals. A valid model of anxiety? Eur. J. Pharmacol. 463, 133-143.

60. Sánchez C, Bergqvist PBF, Brennum LT, Gupta S, Hogg S, Larsen AK and Wiborg O (2003). Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. Psychopharmacology. 167, 353-362.

61. Sánchez C, Gruca P, Bien E, Papp M (2003). R-citalopram attenuates the antidepressant-like effect of escitalopram in a rat chronic mild stress model of depression. Behav. Pharmacol. 14, 465-470.

62. Sánchez C, Gruca P, Bien E, Papp M (2003). R-citalopram counteracts the anxiolytic-like effect of escitalopram in a rat conditioned fear stress model of anxiety. Pharmacol. Biochem. Behav. 73, 903-907.

63. Voss J, Sanchez C, Ebert B (2003). Interaction of the $GABA_A$ receptor agonist gaboxadol with benzodiazepines measured in the rotarod model. Eur. J. Pharmacol. 482, 215-222.

64. Voss J, Sanchez C, Michelsen S, Ebert B. (2003) Rotarod studies in the rat of the GABAA receptor agonist gaboxadol: lack of ethanol potentiation and benzodiazepine cross-tolerance. Eur J Pharmacol. Dec 15;482(1-3):215-22.

65. Braestrup C, Sanchez C (2004) Escitalopram: A unique mechanism of action. Int J Psychiatry Clin Pract, 8, 11-13

66. Hansen SL, Sperling BB, Sánchez C (2004). The Impact of $GABA_A$ Receptor Modulators on the Development of Pentylenetetrazole Kindling in Mice. Prog. Neuropsychopharm Biol Psychiatry. 28 (1), 105-113.

67. Hermit MB, Greenwood JR, Nielsen B, Bunch L, Jorgensen CG, Vestergaard HT, Stensbol TB, Sanchez C, Krogsgaard-Larsen P, Madsen U, Brauner-Osborne H. (2004) Ibotenic acid and thioibotenic acid: a remarkable difference in activity at group III metabotropic glutamate receptors.Eur J Pharmacol. Feb 23;486(3):241-50.

68. Husum H, Bolwig TG, Sánchez C, Mathé AA, Hansen S (2004). Levetiracetam prevents changes in levels of brain-derived neurotrophic factor and neuropeptide Y mRNA and of Y1- and Y5-like receptors in the hippocampus of rats undergoing amygdala kindling: implications for antiepileptogenic and mood-stabilizing properties. Epilepsy and Behaviour, Apr 5, (2) 204-215

69. Larsen AK, Brennum LT, Egebjerg J, Sánchez C, Halldin C, Andersen PH (2004). ^{3}H-MADAM binding *in vitro* and *in vivo* – Escitalopram occupies SERT at clinical relevant dosis. *In vitro* and *in vivo* binding of the SERT ligand ^{3}H-MADAM. Br J pharmacol. 141, 1015-1023.

70. Nedergaard P, Sanchez C, Mellerup E. (2004)Different roles of 5-HT2A and 5-HT2C receptors in regulation of female rat paced mating behaviour. Behav Brain Res. Mar 2;149(2):151-7.

71. Sánchez C, Bøgesø KP, Ebert B, Reines EH, Braestrup C (2004). Escitalopram versus citalopram: the surprising role of the R-enantiomer. Psychopharmacology. 174, 163-176.

72. Sanchez C, Kreilgaard M. (2004) R-citalopram inhibits functional and 5-HTP-evoked behavioural responses to the SSRI, escitalopram. Pharmacol Biochem Behav. Feb;77(2):391-8.

73. Storustovu S, Sanchez C, Porzgen P, Brennum LT, Larsen AK, Pulis M, Ebert B., (2004) R-citalopram functionally antagonises escitalopram in vivo and in vitro: evidence for kinetic interaction at the serotonin transporter. Br J Pharmacol. May;142(1):172-80. Epub 2004 Mar 22.

74. Chen F, Larsen MB, Neubauer HA, Sanchez C, Plenge P, Wiborg O. Related Articles, (2005) Characterization of an allosteric citalopram-binding site at the serotonin transporter. J Neurochem. Jan;92(1):21-8.

75. Chen F, Larsen MB, Sanchez C, Wiborg O., (2005) The S-enantiomer of R,S-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors. Eur Neuropsychopharmacol. Mar;15(2):193-8.

76. Clausen RP, Moltzen EK, Perregaard J, Lenz SM, Sanchez C, Falch E, Frolund B, Bolvig T, Sarup A, Larsson OM, Schousboe A, Krogsgaard-Larsen P. (2005) Selective inhibitors of GABA uptake: synthesis and molecular pharmacology of 4-N-methylamino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol analogues. Bioorg Med Chem. Feb 1;13(3):895-908

77. El Mansari M, Sanchez C, Chouvet G, Renaud B, Haddjeri N., (2005) Effects of acute and long-term administration of escitalopram and citalopram on serotonin neurotransmission: an in vivo electrophysiological study in rat brain. Neuropsychopharmacology. Jul;30(7):1269-77

78. Connie Sanchez. (2005) The Pharmacology of Citalopram Enantiomers: The Antagonism by R-Citalopram on the Effect of S-Citalopram. Basic & Clinical Pharmacology & Toxicology, vol. 99, issue 2

79. Connie Sánchez,C (2006) The pharmacology of citalopram enantiomers: the antagonism by R-citalopram on the effect of S-citalopram. Basic Clin Pharmacol Toxicol. 2006 Aug; 99(2):91-5, Review

80. Mansari ME, Wiborg O, Mnie-Filali O, Benturquia N, Sanchez C, Haddjeri N. (2006) Allosteric modulation of the effect of escitalopram, paroxetine and fluoxetine: in-vitro and in-vivo studies. Int J Neuropsychopharmacol. Feb 1;:1-10 [Epub ahead of print]

81. Ouissame Mnie-Filali, Mostafa El Mansari, Agn`es Espana, Connie Sanchez, Nasser Haddjeri. (2006) Allosteric modulation of the effects of the 5-HT reuptake inhibitor escitalopram on the rat hippocampal synaptic plasticity. Neuroscience Letters October 395, 23–27

82. Connie Sanchez, (2006) Allosteric modulation of monoamine transporters - new drug targets in depression. Drug Discovery Today: Therapeutic Strategies, Vol. 3, No. 4

83. Sánchez C, Brennumb LT, Stórustovub S, Kreilgård M, Mørk, A, (2007) Depression and poor sleep: the effect of monoaminergic antidepressants in a pre-clinical EEG model in rats. Pharmacology, Biochemistry and Behavior: Pharmacol Biochem Behav. 2007 Jan 18; http://dx.doi.org/10.1016/j.pbb.2007.01.006

84. Jacquot C., DAVID DJ, GARDIER AM, SÁNCHEZ C, Escitalopram et Citalopram : le rôle inattendu de l'énantiomère. (2007) L'Encéphale, 85.33:86. Mars-Avril, cahier 1

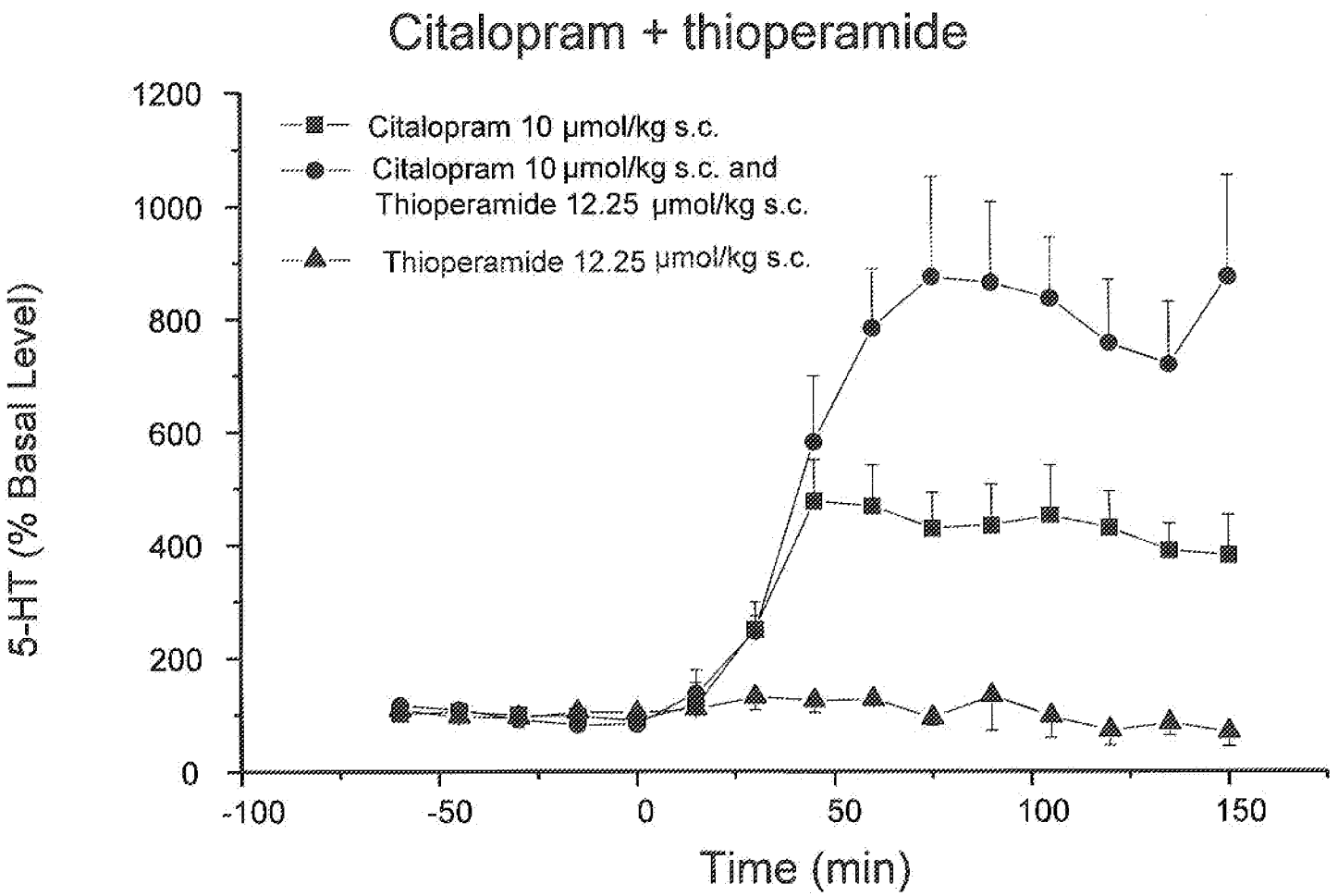
85. Mnie-Filali O, El Mansari M, Scarna H, Zimmer L, Sánchez C, Haddjeri N, (2007) L'escitalopram: un inhibiteur sélectif et un modulateur allostérique du transporteur de la sérotonine. Escitalopram: A selective inhibitor and allosteric modulator of the serotonin transporter. L'Enc´ephale 33, 965—972

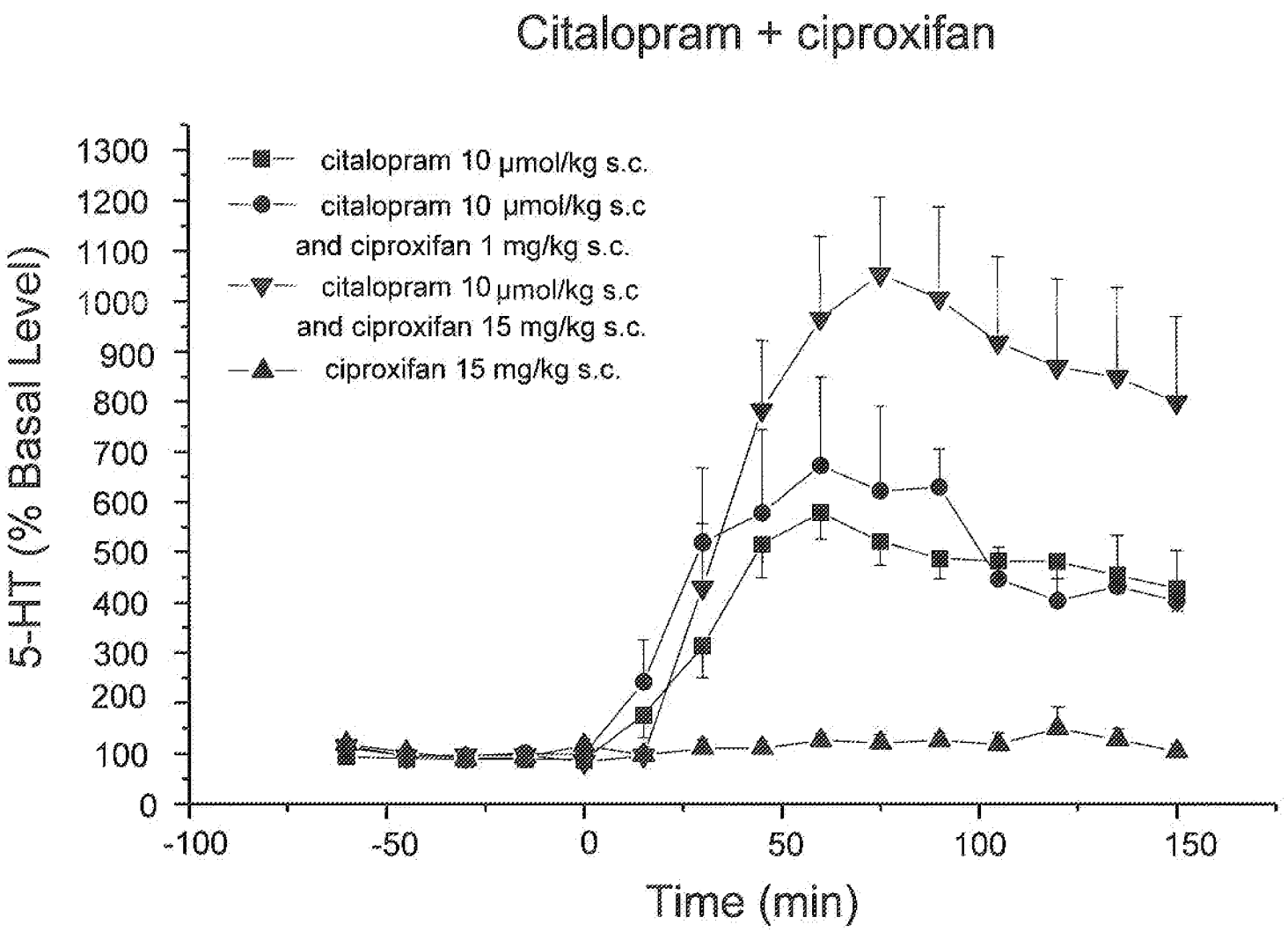
86. Michelsen S, Sánchez C, Ebert B. (2007) Lack of generalisation between the GABAA receptor agonist, gaboxadol, and allosteric modulators of the benzodiazepine binding site in the rat drug discrimination procedure. Psychopharmacology (Berl). Jul;193(1):151-7. Epub 2007 Mar 15.

87. Ebert B, Anderson NJ, Cremers TI, Rasmussen S, Vogel V, Fahey JM, Sánchez C. (2008) Gaboxadol -- a different hypnotic profile with no tolerance to sleep EEG and sedative effects after repeated daily dosing. Pharmacol Biochem Behav. Jul;90(1):113-22. Epub 2008 Feb 5.

88. Kreilgaard M, Smith DG, Brennum LT, Sánchez C. (2008) Prediction of clinical response based on pharmacokinetic/pharmacodynamic models of 5-hydroxytryptamine reuptake inhibitors in mice. Br J Pharmacol. Sep;155(2):276-84. Epub 2008 Jun 16.

89. Zhong H, Hansen KB, Boyle NJ, Han K, Muske G, Huang X, Egebjerg J, Sánchez C. (2009) An allosteric binding site at the human serotonin transporter mediates the inhibition of escitalopram by R-citalopram: Kinetic binding studies with the ALI/VFL-SI/TT mutant. Zhong H, Hansen KB, Boyle NJ, Han K, Muske G, Huang X, Egebjerg J, Sánchez C. Neurosci Lett. Sep 25;462(3):207-212. Epub 2009 Jul 16.


Citalopram + thioperamide
Citalopram 10 µmol/kg s.c.
Citalopram 10 µmol/kg s.c. and
Thioperamide 12.25 µmol/kg s.c.
Thioperamide 12.25 µmol/kg s.c.
5-HT (% Basal Level)
1200
1000
800
600
400
200
0
-100
-50
0
50
100
150
Time (min)


Citalopram + ciproxifan
citalopram 10 µmol/kg s.c.
citalopram 10 µmol/kg s.c
and ciproxifan 1 mg/kg s.c.
citalopram 10 µmol/kg s.c
and ciproxifan 15 mg/kg s.c.
ciproxifan 15 mg/kg s.c.
5-HT (% Basal Level)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-50
0
50
100
150
Time (min)